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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hakan Lomryd, et al.

Title: PHARMACEUTICAL COMPOSITION AS SOLID DOSAGE FORM AND METHOD FOR MANUFACTURING THEREOF

Appl. No.: 10/626,857

Filing Date: July 25, 2003

Examiner: T. PAGE

Art Unit: 1615

LETTER

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Petition to Make Special filed April 25, 2005, Applicants submit herewith Appendix A to the Statement & Detailed Discussion that was inadvertently omitted from the filing. Applicants respectfully request that the petition be granted, and that an indication of allowability be issued as soon as possible.

Please charge any additional fees required by this paper or credit any overpayment to Deposit Account No. 19-0741.

Respectfully submitted,

Date April 26, 2005

By Courtenay C. Brinckerhoff

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002.1383822.1

APPENDIX A

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Europäisches Patentamt	European Patent Office	Office européen des brevets
Generaldirektion 2	Directorate General 2	Direction Générale 2

HOFFMANN EITLE
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München
ALLEMAGNE

Application No.	Ref.	Date
03 016 945.2 - 1219	103080-PEP	18.04.2005
Applicant: Ferring B.V.		

Communication under Rule 51(4) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

In the text for the Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR

Description, Pages

5-7, 11, 13-15	as originally filed
1-4, 8-10, 12	received on 12.07.2004 with letter of 12.07.2004

Claims, Numbers

1-15, 20-36	received on 04.05.2004 with letter of 29.04.2004
16-19, 37	received on 12.07.2004 with letter of 12.07.2004

Drawings, Sheets

2	as originally filed
1	received on 12.07.2004 with letter of 12.07.2004

With the following amendments to the above-mentioned documents according to your request dated 01.10.2004 :

Claims, Numbers 19§

With the following amendments to the above-mentioned documents by the examining division

Description, Pages 5,13*

Registered Letter
EPO Form 2004 04.05CSX

Comments

*...page 5, line 22-23 deleted; page 13, lines 5-6 deleted: Article 84 EPC.
§...Claim 38 deleted; see Minutes of telephone interview of 1 October 2004.

A copy of relevant documents is enclosed

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name of the applicant and the bibliographic data are shown on the attached EPO Form 2056.

You are requested within a **non-extendable** period of four months of notification of this communication

1. to file 1 set of translations of the claim(s) in the two other EPO official languages;

		EUR
2a.	to pay the fee for grant including the fee for printing up to and including 35 pages; Reference 007	715.00
2b.	to pay the printing fee for the 36th and each additional page; number of pages: 0 Reference 008	0.00
3.	to pay the additional claim fee(s) (Rule 51(7) EPC); number of claims fees payable: 0 Reference 016	0.00
	Total amount	715.00

Concerning the possibility of a request for accelerated grant pursuant to Article 97(6) EPC, reference is made to OJ EPO 2001, 459.

If the grant, printing or claims fees are not paid, or the translations not filed, in due time the European patent application will be deemed to be withdrawn (Rule 51(8) EPC).

For all payments you are requested to use EPO Form 1010 or to refer to the relevant reference number.

After publication, the European patent specification can be downloaded free of charge from the EPO publication server https://publications.european-patent-office.org or ordered only from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

Upon request in writing each proprietor will receive the certificate for the European patent **together with one copy** of the patent specification only if the request is filed within the time limit of Rule 51(4) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 51(4) EPC. The requested copy is free of charge. If the request is filed after expiry of the Rule 51(4) EPC time limit, the certificate will be delivered without a copy of the patent specification.

Translation of the priority document(s)

If the translation of the priority document(s), as required by Article 88(1) EPC, or the declaration according to Rule 38(5) EPC has not yet been filed, Form 2530 will be despatched separately. The translation is to be filed within the above mentioned time limit (Rule 38(5) EPC).

Note on payment of renewal fees

If a renewal fee falls due between notification of the present communication and the proposed date of publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (Rule 51(9) EPC).

Under Article 86(4) EPC, renewal fees are payable to the European Patent Office until the year in which the mention of the grant of the European patent is published.

Filing of translations in the Contracting States

Pursuant to Article 65(1) EPC the following Contracting States require a translation of the specification of the European patent in their/one of their official language(s) (Rule 51(10) EPC), **insofar** this specification will not be published in their/one of their official language(s)

- within **three** months of publication of the mention of such decision:

AT	AUSTRIA	GB	UNITED KINGDOM
BE	BELGIUM	GR	GREECE
BG	BULGARIA	HU	HUNGARY
CH	SWITZERLAND / LIECHTENSTEIN	IT	ITALY
CY	CYPRUS	NL	NETHERLANDS
CZ	CZECH REPUBLIC	PT	PORTUGAL
DE	GERMANY	RO	ROMANIA
DK	DENMARK	SE	SWEDEN
EE	ESTONIA	SI	SLOVENIA
ES	SPAIN	SK	SLOVAKIA
FI	FINLAND	TR	TURKEY
FR	FRANCE		

- within **six** months of publication of the mention of such decision:

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The date on which the European Patent Bulletin publishes the mention of the grant of the European patent will be indicated in the decision on the grant of the European patent (EPO Form 2006).

In case of a valid extension the following Extension States require a translation of the **claims** in their official language within **three** months after publication of the mention of the grant of the European patent:

LT	LITHUANIA	LV	LATVIA

The translation must be filed with the national Patent Offices of the Contracting or Extension States in accordance with the provisions applying thereto in the State concerned. Further details (e.g. appointment of a national representative or indication of an address for service within the country) are given in the EPO information brochure "National law relating to the EPC", and in the supplementary information published in the Official Journal of the EPO, or available on the EPO website.

Failure to supply such translation to the Contracting and Extension States in time and in accordance with the requirements may result in the patent being deemed to be void ab initio in the State concerned.

Note to users of the automatic debiting procedure

Unless the EPO receives prior instructions to the contrary, the fee(s) will be debited on the last day of the period of payment. For further details see the Arrangements for the automatic debiting procedure (see Supplement to OJ EPO 2, 2002).

Registered Letter
EPO Form 2004 04.05CSX

Examining Division:

Chairman:	Boulois, D
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Enclosure(s): Form 2056
23 Copies of the relevant documents

Registered Letter
EPO Form 2004 04.05CSX

ADDITIONAL SHEET +++ IMPORTANT INFORMATION +++

1. **For communications under Rule 51(4) EPC issued on or after 01.04.2005 the time limit of four months is not extendable anymore:**

   According to Rule 51(4) EPC as amended the time limit set in the communication under Rule 51(4) EPC will be four months in all applications without possibility of extension.

   Amended Rule 51(4) EPC applies to all applications for which a communication under Rule 51(4) EPC is issued on or after 01.04.2005.

2. **A copy of the patent specification will only be annexed to the European Patent certificate upon special request within the time limit of the 51(4) EPC communication:**

   Under Rule 54 EPC as amended and the decision of the President of the EPO dated 22.12.2004 (OJ EPO 2005, 122) each proprietor will receive the certificate for the European patent together with a copy of the patent specification upon request in writing and only if the request is filed within the time limit of Rule 51(4) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 51(4) EPC. The requested copy is free of charge.

   If the request is filed after expiry of the Rule 51(4) EPC time limit, the certificate will be delivered without a copy of the patent specification.

   After publication, the European patent specification can be downloaded free of charge from the EPO publication server https://publications.european-patent-office.org or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

   As before, upon payment of an administrative fee a duplicate copy of the European patent certificate with the patent specification attached or a certified copy of the patent specification will also be supplied.

CLAIMS

1. A pharmaceutical composition as a solid dosage form comprising desmopressin, or a pharmaceutically acceptable salt thereof, as a therapeutically active ingredient together with a pharmaceutically acceptable excipient, diluent or carrier, or mixture thereof, wherein the pharmaceutical composition is composed of a compressed granulate and contains lubricant in an amount of from 0.05 to 0.40 percent by weight of said pharmaceutical composition.

2. A pharmaceutical composition according to claim 1 which contains lubricant in an amount of from 0.10 to 0.30 percent by weight of said pharmaceutical composition.

3. A pharmaceutical composition according to claim 2 which contains lubricant in an amount of from 0.15 to 0.30 percent by weight of said pharmaceutical composition.

4. A pharmaceutical composition according to any one of claims 1-3 which is compressed of a granulate with an average size of at least 100 µm, preferably in the range of from 100 µm to 2 mm, more preferably in the range of from 100 to 600 µm.

5. A pharmaceutical composition according to claim 4, wherein said granulate has a size distribution where at least 50%, preferably from 50 to 90%, by volume thereof consists of granulate particles with a size of at least 100 µm, preferably in the range of from 100 µm to 2 mm, more preferably in the range of from 100 to 600 µm.

6. A pharmaceutical composition according to any one of claims 1-5, wherein said lubricant is selected from a group consisting of stearic acid, salts or esters of stearic acid, hydrogenated vegetable oils, magnesium oxide, polyethylene glycol, sodium lauryl sulphate and talc, and mixtures thereof.

7. A pharmaceutical composition according to claim 6, wherein said lubricant is selected from magnesium stearate, calcium stearate, zinc stearate, glyceryl palmitostearate and sodium stearyl fumarate, and mixtures thereof.

8. A pharmaceutical composition according to any one of claims 1-7, wherein at least one of said excipient, diluent and carrier is a substance selected from a monosaccharide, disaccharide, oligosaccharide and a polysaccharide.

9. A pharmaceutical composition according to claim 8, wherein the said substance has an average particle size in the range of from 60 to 1 000 µm.

10. A pharmaceutical composition according to claim 9, wherein said average particle size is in the range of from 70 to 500 µm, preferably from 75 to 350 µm, more preferably from 100 to 200 µm, and even more preferably from 120 to 180 µm.

11. A pharmaceutical composition according to any one of claims 8-10, wherein said substance is a disaccharide, preferably lactose, and more preferably lactose-α-monohydrate.

12. A pharmaceutical composition according to any one of claims 8-10, wherein said polysaccharide is a starch, preferably potato starch.

13. A pharmaceutical composition according to any one of claims 8-12, wherein both said disaccharide and polysaccharide are present.

14. A pharmaceutical composition according to claim 13, wherein the weight ratio between said disaccharide and polysaccharide is from 100:1 to 1:100, preferably from 10:1 to 1:10, and more preferably from 2:1 to 1:2.

15. A pharmaceutical composition according to any one of claims 1-14, wherein the total combined amount of said excipient, diluent and carrier is from 5 to 99, preferably from 50 to 99, percent by weight of the pharmaceutical composition.

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16. A pharmaceutical composition according to any one of claims 1-15, wherein said solid dosage form is a perorally available tablet that is optionally adapted for oromucosal, preferably buccal and/or sublingual, administration.

17. A pharmaceutical composition according to any one of claims 1-16, which comprises desmopressin acetate in an amount of from 20 to 600 µg per unit of solid dosage form.

18. A pharmaceutical composition according to any one of claims 1-17, wherein each unit of solid dosage form has a hardness of at least ~~5 kp~~ 49 N (5 kp).

19. A method for the manufacturing of a pharmaceutical composition as a solid dosage form comprising desmopressin, or a pharmaceutically acceptable salt thereof, as a therapeutically active ingredient, wherein said method comprises the steps of:

i) mixing desmopressin and an excipient, diluent or carrier, or mixture thereof, optionally in the presence of a wetting agent;

ii) subjecting the resulting mixture to formation of a granulate, optionally in the presence of a wetting agent, suitable for compression into said solid dosage form;

iii) optionally performing said mixing and/or formation of a granulate in the presence of at least one additive selected from a disintegrating agent, binder, flavoring agent, preservative, colorant and a mixture thereof;

iv) optionally drying said granulate;

v) compressing said granulate into said solid dosage form;

wherein lubricant is introduced so that the resulting pharmaceutical composition contains lubricant in an amount of from 0.05 to ~~less than 6.5~~ 4 0.40 percent by weight of said pharmaceutical composition.

20. A method according to claim 19, wherein the pharmaceutical composition contains lubricant in an amount of from 0.10 to 0.30 percent by weight of said pharmaceutical composition.

21. A method according to claim 20, wherein the pharmaceutical composition contains lubricant in an amount of from 0.15 to 0.30 percent by weight of said pharmaceutical composition.

22. A method according to any one of claims 19-21, wherein said resulting mixture is subjected to formation of a granulate with an average size of a least 100 µm, preferably in the range of from 100 µm to 2 mm, more preferably in the range of from 100 to 600 µm.

23. A method according to claim 22, wherein said formation of granulate provides a size distribution where at least 50%, preferably from 50 to 90%, by volume of said granulate consists of granulate particles with a size of at least 100 µm, preferably in the range of from 100 µm to 2 mm, more preferably in the range of from 100 to 600 µm.

24. A method according to any one of claims 19-23, wherein said lubricant is selected from a group consisting of stearic acid, salts or esters of stearic acid, hydrogenated vegetable oils, magnesium oxide, polyethylene glycol, sodium lauryl sulphate and talc, and mixtures thereof.

25. A method according to claim 24, wherein said lubricant is selected from magnesium stearate, calcium stearate, glyceryl palmitostearate, sodium stearyl fumarate and zinc stearate, and mixtures thereof.

26. A method according to any one of claims 19-25, wherein at least one of said excipient, diluent and carrier is a substance selected from a monosaccharide, disaccharide, oligosaccharide and a polysaccharide.

27. A method according to claim 26, wherein said substance has an average particle size in the range of from 60 to 1 000 µm.

28. A method according to claim 27, wherein said average particle size is in the range of from 70 to 500 µm, preferably from 75 to 350 µm, more preferably from 100 to 200 µm, and even more preferably from 120 to 180 µm.

29. A method according to any one of claims 26-28, wherein said substance is a disaccharide, preferably lactose, and more preferably lactose-α-monohydrate.

30. A method according to any one of claims 26-28, wherein said polysaccharide is a starch, preferably potato starch.

31. A method according to any one of claims 19-30, wherein said solid dosage form is a perorally available tablet that is optionally adapted for oromucosal, preferably buccal and/or sublingual, administration.

32. A method according to any one of claims 19-31, wherein said steps of mixing and formation of a granulate are performed in a single integrated machinery that is adapted for such a combined process.

33. A method according to any one of claims 19-32, wherein said wetting agent is selected from water and a mixture of water and an alcohol, preferably ethanol.

34. A method according to any one of claims 19-33, wherein both said disaccharide and polysaccharide are present in the mixing step.

35. A method according to claim 34, wherein the weight ratio between said disaccharide and polysaccharide is from 100:1 to 1:100, preferably from 10:1 to 1:10, and more preferably from 2:1 to 1:2.

36. A method according to any one of claims 19-35, wherein the total combined amount of said excipient, diluent and carrier is from 5 to 99, preferably from 50 to 99, percent by weight of the pharmaceutical composition.

~~37. A method according to any one of claims 19-36,~~ wherein desmopressin ~~acetate is used~~ and mixed with the ~~excipient, diluent or carrier in an amount that provides~~ H

37. A method according to any one of claims 19-36, wherein desmopressin acetate is used and mixed with the excipient, diluent or carrier in an amount that provides from 20 to 600 µg of desmopressin acetate per unit of solid dosage form.

~~38. A method according to any one of claims 19-37, wherein each unit of solid dosage form is compressed to a hardness of at least 5 kp.~~

~~3839. A pharmaceutical composition as a solid dosage~~ form that is obtainable by a ~~method~~ as defined in any one ~~of claims 19-3837.~~